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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,040	12/30/2005	Brian G. Van Ness	09531-109US1	9035

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
09/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/532,040	VAN NESS ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *9-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the restriction/election requirement received on 5/28/08 has been entered. Claims 1-22 are pending in the instant application. Applicant's election of Group I, and the species Bcl-xl without traverse is acknowledged. Claims 9-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/28/08. Claims 1-8 are therefore currently under examination. An action on the merits follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a transgene comprising an immunoglobulin kappa 3' enhancer operatively linked to a cDNA encoding Bcl-xL, wherein mature and plasma B cell populations of the transgenic mouse are expanded, does not reasonably provide enablement for making or using any transgenic rodent whose genome comprises a transgene comprising an immunoglobulin kappa 3' enhancer operatively linked to a cDNA encoding Bcl-xL, wherein mature and plasma B cell populations of the transgenic rodent are expanded The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims as written are broadly drawn to transgenic rodents, or cells derived from a transgenic rodent. The order Rodentia includes more than 2000 species including not only murine species such as rats and mice, but squirrels, porcupines, beavers, marmots, gophers, and prairie dogs too. The specification, while broadly referring to the generation of transgenic rodents, is primarily drawn to the generation of transgenic mice and does not provide any specific guidance for making transgenic rodents from such diverse species as porcupines, beavers, squirrels, or prairie dogs. However, the state of the art of making transgenic animals, including rodents, was considered unpredictable at the time of filing. At the time of filing, the art teaches two basic methods for generating transgenic or knock-out animals: 1) microinjection of embryos, and 2) genetic modification of embryonic stem cells. The literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations. The primary problem in microinjection is the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression and/or cause unpredictable levels of transgene expression based on the proximity of the transgene to regulatory elements such as enhancers or silencers (Wigley et al. (1994) Reprod. Fertil. Dev., Vol. 6, 585-588, Mullins et al. (1996) J. Clin. Invest., Vol. 98(11), S37-S40, Wall (1996) Theriogenology, Vol. 45, 57-68). While targeted integration of transgenes in embryonic stem cells overcomes a number of the limitations associated with microinjection, at the time of filing, embryonic stem cells had not been isolated for species other than mouse. Campbell et al. teaches that, "[i]n species other than the mouse the isolation of ES cells has proved more difficult. There

are reports of ES-like cell lines in a number of species....However, as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse" (Campbell et al. (1997)Theriogenology, Vol. 47 (1), page 65, paragraph 2). The specification does not provide any guidance concerning the use of non-mouse embryonic stem cells to make any non-mouse transgenic rodent or overcome the lack of predictability in the art for making any transgenic rodent such as a transgenic squirrel, porcupine, or marmot, using microinjection techniques. As such, in view of the lack of specific guidance for making any type of transgenic rodent other than a mouse, the limitation of the working examples to transgenic mice, the state of the art of making transgenic animals, and the breadth of the claims, it would have required undue experimentation to make and use any transgenic rodent as claimed other than a transgenic mouse.

In addition, regarding the claimed phenotype of an expanded mature and plasma B cell population, the specification provides a working example demonstrating that transgenic mice comprising a Bcl-xl transgene under transcriptional control of the Ig kappa 3' enhancer and kappa promoter exhibit increased numbers of mature B cells and plasma cells. The working examples do not disclose the phenotype of any other transgenic rodent comprising the same or a similar transgene. While the specification, as noted, exemplifies a transgenic mouse with the claimed phenotype, the state of the art of transgenic at the time of filing was such that the skilled artisan would not have been able to predict whether other species of rodents comprising the same or a similar transgene would have the same phenotype as the disclosed mice. In particular, the prior art teaches that the expression of the same gene in different animal species can result in different phenotypes. For example, Mullins teaches that while transgenic rats expressing a Ren-2

gene or HLA B27 exhibit high blood pressure or spontaneous inflammatory disease respectively, the expression of the same genes in mice produced no phenotype (Mullins, *supra,* page S38). Thus, the skilled artisan would not have been able to predict without undue experimentation whether the expression of Bcl-xL in any non-mouse rodent species would be the same as that observed in the disclosed transgenic mice and produce the same phenotype of expanded mature and plasma B cell populations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grillot et al. (1996) J. Exp. Med., Vol. 183, 381-391, in view of Adams et al. (1985) Nature, Vol. 318, 533-538. The applicant claims a transgenic rodent whose nucleated cells comprise a transgene comprising an immunoglobulin (Ig) kappa light chain 3' enhancer sequence operably linked to a nucleic acid sequence encoding Bcl-xL, wherein the rodent exhibits expanded plasma cell and mature B cell populations compared to wild type rodents. The applicant further claims said rodent which is a mouse and wherein the Bcl-xL is human Bcl-xL. The applicant also claims isolated cells from the transgenic rodent, and specifically a B lineage plasma cell.

Grillot et al. teaches transgenic mice whose genome, and therefore nucleated cells, comprises a transgene comprising an SV40 promoter and Ig heavy chain enhancer operatively linked to a cDNA encoding human Bcl-xl, and which exhibits a phenotype comprising enhanced survival and increased accumulation of mature B cells compared to wild-type mice (Grillot et al, pages 382 and 387). Grillot et al. further teaches the isolation of various B cells lineages from Bcl-xl transgenic mice (Grillot et al., page 382).

Grillot et al. differs from the claimed invention by using an Ig heavy chain enhancer instead of an Ig kappa 3' enhancer. Adams et al. supplements the teachings of Grillot et al. by teaching that both the Ig heavy chain enhancer and the Ig kappa chain enhancer are effective in

driving B cell specific heterologous transgene expression in transgenic mice (Adams et al., pages 533-534 and 537). Therefore, based on the evidence provided by Adams et al., that the Ig kappa chain enhancer functions similarly to the Ig heavy chain enhancer in directing B cell specific expression of heterologous transgenes in transgenic mice, it would have been *prima facie* obvious to the skilled artisan at the time of filing to substitute the Ig kappa enhancer taught by Adams et al. for the Ig heavy chain enhancer in the constructs for making a transgenic mouse according to Grillot et al. with a reasonable expectation of success in using such a construct to produce a transgenic mouse exhibiting a phenotype of expanded mature B cells and plasma cell populations, as such a replacement represents nothing more than simple substitution of one known element for another to obtain predictable results.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Grillot et al. (1996) J. Exp. Med., Vol. 183, 381-391, in view of Adams et al. (1985) Nature, Vol. 318, 533-538, applied to claims 1-7 above, and further in view of Miller et al. (1992) Immunogenetics, Vol. 35, 24-32. The applicant claims a transgenic rodent whose nucleated cells comprise a transgene comprising an immunoglobulin (Ig) kappa light chain 3' enhancer sequence and kappa promoter operably linked to a nucleic acid sequence encoding Bcl-xL, wherein the rodent exhibits expanded plasma cell and mature B cell populations compared to wild type rodents.

The teachings of Grillot et al. and Adams et al. are set forth above. While Grillot et al. and Adams render obvious a transgenic mouse whose genome comprises a transgene comprising an Ig kappa enhancer operably linked to a human cDNA encoding Bcl-xl, neither Grillot et al. or Adams et al. teaches to use an Ig kappa promoter to drive transcription of Bcl-xl. It is noted that

both Grillot et al. and Adams et al. utilized an SV40 promoter. Miller et al. further supplements Grillot et al. and Adams et al. by teaching that the Ig kappa promoter can be used in combination with an Ig enhancer to drive B cell lineage specific expression of a heterologous transgene in transgenic mice (Miller et al., pages 25 and 27-28). Thus, based on the evidence provided by Miller et al. that the Ig kappa promoter in combination with an Ig enhancer can be used successfully to drive expression of a heterologous transgene in B cells of a transgenic mouse, and the evidence provided by Adams et al., that the Ig kappa chain enhancer functions similarly to the Ig heavy chain enhancer in directing B cell specific expression of heterologous transgenes in transgenic mice, it would have been *prima facie* obvious to the skilled artisan at the time of filing to substitute the Ig kappa enhancer taught by Adams et al. for the Ig heavy chain enhancer in the constructs for making a transgenic mouse according to Grillot et al. and the Ig kappa promoter taught by Miller et al. for the SV40 promoter in the constructs for making a transgenic mouse according to Grillot et al. to produce a transgene construct comprising an Ig kappa enhancer and promoter operatively linked to a human cDNA encoding Bcl-xL with a reasonable expectation of success in using such a construct to produce a transgenic mouse exhibiting a phenotype of expanded mature B cells and plasma cell populations, as such replacements represents nothing more than simple substitution of one known element for another to obtain predictable results.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not

available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633